

factor-alpha neutralizing antibody or pretreatment with cyclophosphamide abolished plug-induced EGFR protein expression and *goblet* *cell* *metaplasia*. Thus instillation of agarose plugs induces profound *goblet* *cell* *metaplasia* by causing EGFR expression and activation.

5/3,K/6 (Item 6 from file: 5)
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Epidermal growth factor system regulates mucin production in airways.

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ABSTRACT: *Goblet*-*cell* hyperplasia is a critical pathological feature in hypersecretory diseases of airways. However, the underlying mechanisms are unknown, and no effective therapy exists. Here we show that stimulation of epidermal *growth* factor receptors (EGF-R) by its ligands, EGF and transforming *growth* factor alpha (TGFalpha), causes MUC5AC expression in airway epithelial cells both in *in vitro* and *in vivo*. We found that a MUC5AC-inducing epithelial cell...

...TNFalpha). EGF-R ligands increased the expression of MUC5AC at both gene and protein levels, and this effect was potentiated by TNFalpha.

Selective EGF-R *tyrosine* *kinase* *inhibitors* blocked MUC5AC expression induced by EGF-R ligands. Pathogen-free rats expressed little EGF-R protein in airway epithelial cells; intratracheal instillation of TNFalpha induced EGF-R in airway epithelial cells, and subsequent instillation of EGF-R ligands increased the number of *goblet* *cells*, Alcian blue-periodic acid-Schiff staining (reflecting mucous glycoconjugates), and MUC5AC gene expression, whereas TNFalpha, EGF, or TGFalpha alone was without effect. In sensitized rats, three intratracheal instillations of ovalbumin resulted in EGF-R expression and *goblet*-*cell* production in airway epithelium. Pretreatment with EGF-R *tyrosine* *kinase* *inhibitor*, BIBX1522, prevented *goblet*-*cell* production both in rats stimulated by TNFalpha-EGF-R ligands and in an asthma model. These findings suggest potential roles for inhibitors of the EGF...

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IL-13 induces mucin production by stimulating epidermal growth factor receptors and by activating neutrophils

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Mucus hypersecretion contributes to the morbidity and mortality in acute

asthma. Both T helper 2 (Th2) cytokines and epidermal *growth* factor receptor (EGFR) signaling have been implicated in allergen-induced *goblet* *cell* (GC) *metaplasia*. Present results show that a cascade of EGFR involving neutrophils is implicated in interleukin (IL)-13-induced mucin expression in GC. Treatment with a selective EGFR *tyrosine* *kinase* *inhibitor* prevented IL-13-induced GC *metaplasia* dose dependently and completely. Instillation of IL-13 also induced tumor necrosis factor-a protein expression, mainly in infiltrating neutrophils. Control airway epithelium contained few...

... inhibitor of leukocytes in the bone marrow (cyclophosphamide) or with a blocking antibody to IL-8 prevented both IL-13-induced leukocyte recruitment and GC *metaplasia*. These findings indicate that EGFR signaling is involved in IL-13-induced mucin production. They suggest a potential therapeutic role for inhibitors of the EGFR...

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Mechanisms of Airway Hypersecretion and Novel Therapy(*)

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... have focused the present studies on the mechanism of goblet cell formation (rather than degranulation).

We hypothesized that a growth factor could be involved in *goblet* *cell* production, because hypersecretory diseases are associated with abnormal epithelial *growth* and *proliferation*. A possible candidate is epidermal *growth* factor (EGF) and its receptor EGF-R. EGF-R, a 70-kd membrane glycoprotein, is expressed in fetal airways, where it is important in cell *proliferation*, branching morphogenesis, and epithelial cell differentiation.(9) In healthy adult human airways, expression of EGF-R is sparse, but EGF-R is expressed in malignant...

...by tumor necrosis factor (TNF)-(Alpha) in lungs in hypersecretory diseases.(11) Therefore, we hypothesized that the EGF-R system could play a role in *goblet* *cell* production in disease. We found that stimulation of airway epithelial cells with TNF-(Alpha) induces EGF-R in epithelial cell cultures and in rats *in vivo*.(8) Further, we showed that stimulation of EGF-R by its ligands results in mucus-producing *goblet* *cells*, and that ovalbumin (OVA) sensitization in rats causes induction of EGF-R and *goblet* *cell* production in rat airways. A key discovery is that selective EGF-R *tyrosine* *kinase* *inhibitors* prevent mucus production in each of these systems. We suggest that inhibitors of EGF-R could be useful in preventing *goblet* *cell* production and thus hypersecretion in disease. The studies are reported in detail elsewhere.(8) Only the *in vivo* studies are reported here.

MATERIALS AND METHODS...by instillation of OVA into the airways resulted in the expression of EGF-R in the epithelium and the conversion of epithelial cells to the *goblet* *cell* phenotype. Most interestingly, a selective *inhibitor* of EGF-R *tyrosine* *kinase* completely *inhibited* *goblet* *cell* production in rats stimulated with TNF-(Alpha) plus an EGF-R ligand or sensitized with OVA. These results incriminate EGF-R activation in *goblet* *cell* *metaplasia*.

Previous studies showed that various stimuli such as ozone,(15) sulfur dioxide,(16) viruses,(16) lipopolysaccharide(15,17) and platelet-activating factor(12) up-regulate...

...is described elsewhere.(14)

In summary, the EGF-R cascade is shown by the present studies to be important in stimulating the growth of airway *goblet* *cells*, which are

implicated in mucus hypersecretion, especially in peripheral airways where lesions are difficult to detect and potentially lethal. Treatment with selective *inhibitors* of EGF-R *tyrosine* *kinase* may provide effective therapy in hypersecretory diseases of airways.

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